REMARKS

In view of the following Remarks, the Examiner is requested to withdraw the rejection and allow Claims 27-34 and new claims 45-74, the only claims pending and currently under examination in this application.

FORMAL MATTERS:

Claims 5-26 and 37-44 are canceled without prejudice.

Claims 27, 29, 30, 31, and 34 are amended. Claims 29 and 34 are amended to correct informalities. Claims 27, 30 and 31 are amended to clarify the language of the claim. Support for these amendments may be found throughout the specification as originally filed, for example, to Claim 27, at page 17, lines 2-14; to Claim 30, at page 18, lines 19-24; and to Claim 31, at page 20, lines 13-16.

Claims 45-74 are added. Support for these claims may be found throughout the specification and the claims as originally filed, for example, for Claims 45, 56, and 69, at page 7, lines 6-8; for Claims 46, 57 and 70, at page 19, lines 14-15; for Claims 47, 58 and 71, at page 19, lines 18-20; for Claim 48, at page 8, lines 17-23; for Claims 49, and 62, at page 9, lines 1-3; for Claims 50 and 63, in Claim 13 as originally filed; for Claims 51 and 64, at page 18, lines 19-24; for Claims 52 and 65, at page 20, lines 13-16; for Claims 53 and 66, at page 11, lines 14-17; for Claims 54 and 67, at page 17, lines 21-24; for Claims 55 and 68, at page 17, lines 17-18; for Claim 59, at page 23, lines 28-32; for Claim 60, at page 19, lines 29-31; for Claim 61, at page 20, lines 4-8 and lines 23-32; for Claim 72, at page 23, lines 28-32; for Claim 73, at page 20, lines 21-25; and for Claim 74, at page 20, lines 23-25 and in the examples.

The Specification is amended to include an abstract.

No new matter is added. As such, the Examiner is requested to enter the above amendments.

OBJECTIONS TO THE SPECIFICATION

The abstract of the disclosure is objected to because it uses the PCT abstract.

Applicants herein amend the specification to incorporate an abstract at the end of the specification. In view of this amendment, this objection may be withdrawn.

REJECTIONS UNDER §101

Claims 27-34 are rejected under 35 U.S.C. 101 because the claimed invention allegedly lacks patentable utility. The Examiner asserts that "[t]he claimed method of making a non-cellular library from a set of known collections of nucleic acids e.g., EST (expressed sequence

tags) produces an intermediate product (library), which do not have a specific, disclosed utility." (page 4, lines 16-19)

Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce two or more amplified pooled collections; and (c) combining said two or more amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library has a sequence representation profile that is substantially the same as said initial sequence representation profile." The specification teaches that a nucleic acid library is "a collection of nucleic acids, where each constituent nucleic acid member of the library is of known sequence and corresponds to a known chromosomal transcript" (p. 6, l. 30-32) The specification and the art provide numerous examples of nucleic acid libraries finding use as tools in scientific research. Accordingly, a method for making nucleic acid libraries also has a valuable utility.

The Examiner asserts on page 5, lines 21-29, that:

> The method has no patentable utility since it simply collects data from a known collection of data and dividing it into smaller portions to obtain the initial compound from which the (fragment) sets are derived/obtained. It is not apparent from the specification Examples of any specific utility for the claim method. Even assuming that a library is obtained still the library, an intermediate product, has to undergo screening in the hope that the obtained product has a patentable utility.

Moreover, the Examiner asserts on page 6, lines 14 that:

> The claimed DNA library of plasmids can be used only to gain further information about the underlying genes. The claimed DNA library themselves are not an end of [applicant's] research effort, but only tools to be used along the way in the search for a practical utility. Applicants do not identify the function for the underlying DNA library of non-cellular nucleic acids.

Applicants note that, as discusses above, the specification teaches that a nucleic acid library is "a collection of nucleic acids, where each constituent nucleic acid member of the library is of known sequence and corresponds to a known chromosomal transcript" (p. 6, l. 30-32) Hence, and contrary to the Examiner's assertions, the pending claimed methods are *not* for "simply collect[ing] data from a known collection of data and dividing it into smaller portions to

obtain the initial compound from which the fragment sets are derived/obtained," but rather for the production of a composition of matter, i.e. a collection of nucleic acids, where each constituent nucleic acid member of the library is of known sequence and corresponds to a known chromosomal transcript, wherein the collection has a sequence representation profile that is substantially the same as said initial sequence representation profile.

Furthermore, and contrary to the Examiner's assertions, nucleic acid libraries do have a patentable utility in and of themselves, namely as tools that enable researchers to analyze the roles of nucleic acids represented therein in modulating various biological processes, e.g., cellular growth, sensitivity to infectious agents or chemical substances, the ability of a cell to differentiate, cell morphology, cellular response to changes in the environment, etc. This utility is asserted in the subject patent specification, page 20, line 30 - page 22, l. 32, and an exemplary use for one such nucleic acid library produced by the pending claimed method is set forth in great detail on page 32, line 24 – page 41, line 27. In this working example, Applicants identified a problem to be solved, namely identifying the mechanistic basis of cellular sensitivity to anthrax, and then uses a nucleic acid library produced by the claimed method for its investigation. Accordingly, the product of the claimed method is a research tool which finds use in, for example, screening assays to analyze nucleic acids for their roles as candidate agents in modulating biological processes.

With regard to research tools, in particular research tools in the context of screening assays, the MPEP is very instructive. Specifically at MPEP § 2107.01, Part I, the MPEP states:

Research Tools

Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

Thus, the MPEP dictates that "*screening assays*, and nucleotide sequence techniques *have a clear, specific and unquestionable utility*". Applicants respectfully submit that if screening assays themselves have utility, so, too must libraries used in those screening assays and methods for making such libraries. Furthermore, since the instant claims are directed to methods of making tools useful in screening assays, the subject matter of the instant claims, i.e. methods of making the libraries used in these assays, must, too, have a clear, specific and unquestionable utility.

Further, the Federal Circuit has emphasized the importance to biotechnology of patenting research tools. In *Integra Lifesciences I, Ltd. v. Merck KGaA* (Fed. Cir. 2003) 02-1052, 02-1065, it was stated that "*patented tools often facilitate general research to identify candidate drugs*, as well as downstream safety-related experiments on those new drugs." (emphasis added)

Even Judge Newman's dissent in this case maintained the importance of patenting research tools, stating that "A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device (as in *Madey v. Duke University*), or a biochemical method such as the PCR (polymerase chain reaction). It is as subject to the patent right as is any other device or method, whether it is used

to conduct research or for any other purpose. *Use of an existing tool in one's research is quite different from study of the tool itself*." (emphasis added) Thus, Judge Newman provides a distinction between a product for use in research and a product that can only be the subject of research. Applicants respectfully submit that the nucleic acid libraries produced by the pending claimed method are a research tool and not themselves the subject of investigation. Accordingly, the prevailing case law such as that of *Integra Lifesciences I, Ltd. v. Merck KGaA* supports the Applicant's position that the nucleic acid libraries produced by the pending claimed methods, and hence the pending claimed methods themselves, have a specific, substantial, and credible utility.

Consistent with these arguments, the USPTO has issued a number of patents in the last year alone for methods of making and/or using nucleic acid libraries (see, e.g. US 7,655,791 (February 2, 2010); US 7,635,666 (December 22, 2009); US 7,629,170 (December 8, 2009); US 7,582,446 (September 1, 2009); US 7,576,258 (August 18, 2009); US 7,547,662 (June 16, 2009); US 7,504,216 (March 17, 2009); US 7,488,583 (February 10, 2009)), as well as for nucleic acid libraries themselves (see, e.g., US 7,585,957 (September 8, 2009); US 7,491,531 (February 17, 2009);and US 7,582,446 (September 1, 2009)). Likewise, the Examiner of the instant application, Examiner Wessendorf, has allowed a number of patents drawn to methods of making and/or using nucleic acid libraries (see, e.g. 7,488,590 (February 10, 2009); 7,432,063 (October 7, 2008); 7,416,847 (August 26, 2008); 7,390,619 (June 24, 2008); 7,270,969 (September 18, 2007); 7,122,330 (October 17, 2006); 6,994,982 (February 7, 2006); and 6,897,028 (May 24, 2005). Accordingly, it would not be inconsistent with current USPTO practice to find that the products of the claimed methods, namely, nucleic acid libraries, do in fact have a specific, substantial and credible utility and that, as such, the methods of the pending claims for preparing this products meet the criteria for utility under 35 U.S.C. §101.

Finally, Applicants wish to emphasize that, as discussed above, what is claimed is *a method of making* nucleic acid libraries, not any one particular nucleic acid library itself. Applicants submit that making nucleic acid libraries could, in fact, be the end of an artisan's efforts, if, for example, the artisan worked for a biotechnology company that sold nucleic acid libraries to other scientists. To such an artisan, methods of making nucleic acid libraries that "have a sequence representation profile that is substantially the same as said initial sequence representational profile," as is characteristic of nucleic acid libraries made by the pending claimed method would be of great utility.

Thus, the specification in view of the art provides a specific, substantial and credible utility for the nucleic acid library made by the pending claimed method and, consequently, for the claimed method itself. Reconsideration and withdrawal of the rejection is respectfully requested.

REJECTIONS UNDER §112, ¶1

Claims 27-34 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement.

In making this rejection, the Examiner asserts on page 8, line 16 – page 9, line 3 that:

> The specification fails to describe the genus claim method of producing any kind or type of generic non-cellular nucleic acid library of such enormous scope. A claim to such enormous scope should have a corresponding written description that would lead one skilled to the said enormous genus claim. However, the specification at e.g.., page 11, lines 10-13 merely provides definitions for each of the claim term. The detail description at e.g., page 33 is drawn to an EST library obtained from human genes from IMAGE consortium. The specification also does not describe this consortium from which the EST human genes are obtained.

The Examiner asserts on page 9, line 16-20, that

> It is noted that different organisms will also express different activated transcription factors and the expression level could be biased. Thus, the general statements in the specification are not an adequate written description of the invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

In making this rejection, the Examiner appears to be focused on the scope of what is able to be made by the pending claimed method, i.e. "any kind" of non-cellular nucleic acid library. Applicants respectfully submit that, in view of the teachings in the specification and the level of skill in the art, such a scope is not unduly broad.

The specification teaches at page 9, lines 1-8, that non-cellular nucleic acid libraries produced by methods of the pending claims are made from an initial set of separate nucleic acids, generally DNA. The specification teaches at page 9, lines 20-24, that the initial set of separate nucleic acids is an initial set of distinct nucleic acids of differing sequence, where any two given nucleic acid members in a given set are considered distinct or different if they comprise a stretch of at least 50, usually at least 100, nucleotides in length in which the sequence similarity is less than 95% or lower. The specification teaches at page 16, lines 30-32, that in many embodiments, the initial set of separate nucleic acids used to produce the subject libraries is a set of expressed sequence tags (ESTs). The specification provides a working example in which the initial set of separate nucleic acids is a collection of human ESTs obtained from the IMAGE consortium.

Applicants submit that although the specification only provides a working example using a human EST collection, there is no reason to believe that other sets of separate nucleic acids could not similarly be divided into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplified as pooled collections to produce two or more amplified pooled collections; and (c) combined to produce said non-cellular nucleic acid library, wherein the non-cellular nucleic acid library has a sequence representation profile that is substantially the same as said initial sequence representation profile, as recited by the pending claims. The Examiner has provided no evidence to suggest that nucleic acids other than the ESTs described in the working examples would not be amenable to such manipulation, e.g. pipetting, or amplification, or pipetting again. Absent such evidence, one of ordinary skill in the art would fully expect that sets of other separate nucleic acids could also be used in the pending claimed method, and thus, that non-cellular nucleic acid libraries representative of other sets of separate nucleic acids could, in fact, be generated from any initial set of separate nucleic acids.

Furthermore, it was well within the skill of the ordinarily skilled artisan to acquire such sets of nucleic acids, for example by performing RT-PCR on cells of interest to them and preparing a bacterial library of the cDNAs; or by preparing select nucleic acids individually, e.g. to form a collection of nucleic acids representative of a gene family; or by purchasing one of many commercially available nucleic acid collections, e.g. ESTs from IMAGE or Riken.

Thus, Applicants submit that in view of the art, the specification does, in fact, describe the nucleic acid library that is produced by the pending claimed method in sufficient detail that the one of ordinary skill in the art would reasonably conclude that the inventor had possession of the claimed invention. Reconsideration and withdrawal of the rejection is requested.

Applicants submit that new claims 45-74 are also patentable for at least these reasons.

REJECTIONS UNDER §112, ¶2

Claims 27-34 rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that Claim 27 is indefinite as to the metes and bounds of the element "more". Following the Examiner's suggestion, Applicants have amended the claim to recite "at least."

The Examiner asserts that Claim 34 is vague and indefinite in the recitation of "at least about." Applicants have amended the claim to recite "at least."

In view of these amendments, this rejection may be withdrawn.

REJECTIONS UNDER §102

I. Claims 27-34 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Edwards et al. (7235381).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.,* 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909

(1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce two or more amplified pooled collections; and (c) combining said two or more amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as said initial sequence representation profile." Thus, the methods call for pooling distinct nucleic acids, amplifying the pools, and pooling those amplified pools.

Applicants submit that Edwards et al. does not anticipate the pending claims because Edwards et al. does not disclose amplifying pooled collections of nucleic acids to produce two or more pooled collections, or pooling these pools. Edwards et al. teaches making RNA from various tissues (Example 1) or from 5' ESTs from cDNA or genomic libraries (Example 7), synthesizing cDNA from that RNA (Example 2) and cloning that cDNA (Example 3). Edwards teaches fractionating that cDNA by size and pooling the cDNAs greater than 150bp (Example 4); selecting those cDNAs with a 5' oligo tag (Example 5) and transforming them into bacteria. However, nowhere in Edwards et al's procedure does Edwards et al. disclose amplifying pooled collections of initial sets of nucleic acids, or pooling amplified products; for example, Edwards et al. does not amplify the pools of cDNAs greater than 150bp. Edwards et al. is silent on amplification.

Because Edwards et al. does not disclose every step of the pending claimed method, Edwards et al. cannot anticipate the pending claims. Reconsideration and withdrawal of the rejection is requested.

Applicants submit that new claims 45-74 are also patentable for at least these reasons.

II. Claims 27, 30, 32, 33 and 34 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Chengtao et al. (Chinese Journal of Biochemistry, 1999.)

As discussed above, Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce two or more amplified pooled collections; and (c) combining said two or more amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as said initial sequence representation profile." Thus, the methods call for pooling distinct nucleic acids, amplifying the pools, and pooling those amplified pools.

Applicants submit that Chengtao et al. does not anticipate the pending claims because Chengtao et al. does not disclose any steps of the pending claimed method. Chengtao et al. teaches annealing synthetic single strand DNA to make double strand fragments 2, 6, or 8 , filling in the ends and cutting with enzymes, and ligating into vector VR1012 to form monoclones of 2, 6, or 8 (2.1.1). Chengtao et al. teaches cutting out these DNA fragments from the monoclones with enzymes, and recloning the three different fragments into 1 vector (2.1.2). However, nowhere in Chengtao et al's procedure does Chengtao et al. disclose pooling initial sets of distinct nucleic acids, amplifying the pooled collections, and pooling amplified products; for example, Chengtao et al does not pool the DNA fragments cut from the monoclones, or amplify those fragments, or pool those amplified products. Chengtao et al. is silent on pooling and amplification.

Because Chengtao et al. does not disclose every step of the pending claimed method, Chengtao et al. cannot anticipate the pending claims. Reconsideration and withdrawal of the rejection is requested.

Applicants submit that new claims 45-74 are also patentable for at least these reasons.

III. Claims 27-28, 30 and 32 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Okazaki et al. (Nature, 2002).

As discussed above, Claim 27, from which the remaining pending claims depend, recites a method of producing a non-cellular nucleic acid library, the method comprising: "(a) dividing an initial set of a plurality of separate nucleic acids into at least two pooled collections of nucleic acids having an initial sequence representation profile, wherein each pooled collection includes not more than about 100 distinct nucleic acids; (b) amplifying each of said pooled collections to produce two or more amplified pooled collections; and (c) combining said two or more amplified pooled collections to produce said non-cellular nucleic acid library, wherein said non-cellular nucleic acid library is a collection of separate nucleic acids with a sequence representation profile that is substantially the same as said initial sequence representation profile." Thus, the methods call for pooling distinct nucleic acids, amplifying the pools, and pooling those amplified pools.

Applicants submit that Okazaki et al. does not anticipate the pending claims because Okazaki et al. does not disclose amplifying pools of nucleic acids or pooling amplified pooled collections. Okazaki et al. teaches dividing an initial set of cDNAs into 171,144 clusters based on sequence similarity (paragraph bridging p. 563 and 564), and sequencing cDNAs representative of those clusters. However, nowhere in Okazaki et al's procedure does Okazaki et al. disclose amplifying the pooled collections of initial sets of nucleic acids, or pooling those amplified products. Okazaki et al. is silent on amplification.

Because Okazaki et al. does not disclose every step of the pending claimed method, Okazaki et al. cannot anticipate the pending claims. Reconsideration and withdrawal of the rejection is requested.

Applicants submit that new claims 45-74 are also patentable for at least these reasons.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-285.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 24, 2010

By: /Elizabeth A. Alcamo, Reg. No. 64,133/
Elizabeth A. Alcamo, Ph.D.
Registration No. 64,133

Date: March 24, 2010

By: /Bret E. Field, Reg. No. 37,620/
Bret E. Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\STAN (Stanford)\285\STAN-285_RS to OA of 12-24-2009.doc